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# New and emerging Bruton tyrosine kinase inhibitors for treating mantle cell lymphoma - where do they fit in?

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## New and emerging Bruton tyrosine kinase inhibitors for treating mantle cell lymphoma – where do they fit in?

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**Abstract**

**Introduction:** Despite recent prognostic improvements, mantle cell lymphoma (MCL) remains incurable. Bruton tyrosine kinase (BTK) is a key receptor in B-cell tumorigenesis, and the benefits of the first BTK inhibitor, ibrutinib, are becoming clear in MCL. However, off-target activities, which contribute to ibrutinib-related adverse events, suggest potential for further improvement of this drug class.

**Areas covered:** We systematically interrogated Clinicaltrials.gov for trials containing keywords for BTK and MCL. Published literature for new and emerging BTK inhibitors being investigated in MCL was then identified (PubMed and Embase) and summarized, and placed in the context of treatment guidelines.

**Expert commentary:** Reduced off-target effects of new and emerging covalent, irreversible BTK inhibitors under investigation in patients with MCL offer the potential of improved safety compared with ibrutinib. Efficacy may also be favorable based on trial data for acalabrutinib, which has just been approved in the USA as second-line therapy for MCL. The role of BTK inhibitors in treating MCL will evolve substantially over the coming years as results from a number of trials become available, particularly in relation to potential upfront use and possible synergy with other targeted therapies such as B-cell lymphoma 2, phosphoinositide 3-kinase and checkpoint inhibitors.

**Keywords:** Bruton tyrosine kinase inhibitors; B-cell malignancies; mantle cell lymphoma; efficacy; adverse events; treatment guidelines

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## 1. Introduction

Mantle cell lymphoma (MCL) is classified by the World Health Organization as a B-cell neoplasm with morphological variants of diverse clinical behavior [1]. It is an uncommon malignancy, accounting for around 6% of non-Hodgkin lymphoma (NHL) cases [2]. The incidence of MCL appears to be increasing [3,4], although this may be due to improved diagnosis rather than an increase in the actual frequency of the disease. MCL most commonly occurs in men, with a median age at diagnosis of 68 years [4]. Data support the presence of familial risk factors [5-8] and some environmental risk factors for MCL [6,9], but many associations with environmental factors seen for other NHL types have not been observed for MCL [6]. Survival and relapse rates for MCL have recently improved with the incorporation of novel agents and aggressive upfront therapeutic strategies [10,11]. However, with the possible exception of allograft, MCL is still incurable [12] and a substantial unmet need therefore remains.

Bruton tyrosine kinase (BTK) is a kinase enzyme in the B-cell receptor pathway that is critical for the initiation, survival and progression of B-cell malignancies [13-15]. The unique structure of BTK, which is characterized by a cysteine (Cys-481) within the ATP-binding pocket, has made it an attractive therapeutic target. The first realization of this potential has already materialized with the development of ibrutinib. This first-in-class, irreversible, small-molecule inhibitor of BTK covalently binds to Cys-481 [16] and is indicated for use as second-line therapy in MCL in both the USA (in patients who have received at least one prior therapy) and Europe (in relapsed or refractory disease), based on the positive results of a pivotal phase 2 trial [17,18]. Not surprisingly, numerous additional indications are also being sought for this drug in patients with MCL, including as front-line medication in combination with bendamustine plus rituximab (BR) (NCT01776840).

The clinical benefits of ibrutinib in MCL and other B-cell malignancies are becoming increasingly clear. Nevertheless, the development of additional BTK inhibitors for this disease is warranted owing to off-target inhibition of kinases by ibrutinib [16] that may contribute to the adverse events (AEs) associated with this molecule. These include atrial fibrillation, bleeding, diarrhea, rash, headache and nausea [19-23].

Indeed, data from patients with chronic lymphocytic leukemia (CLL) taking ibrutinib show that AEs are a common reason for treatment discontinuation.[24,25] Here we review the state of new and emerging BTK inhibitors under investigation in patients with MCL, and discuss their potential placement in treatment guidelines.

**2. Materials and methods**

Searches were conducted in Clinicaltrials.gov to identify trials with fields containing key terms for BTK inhibitors (BTK OR Bruton OR Bruton’s OR Brutons) AND MCL (MCL OR mantle). Filters were applied to exclude studies that had been terminated or withdrawn. It is possible that clinical trials not specifically mentioning MCL in either the ‘condition’ or ‘submitted keywords’ fields in Clinicaltrials.gov may include patients with MCL as part of a broader clinical trial population. However, for the purpose of focusing this review, we considered an absence of MCL search terms to indicate a lack of intent by the investigator and/or manufacturer to move forward into MCL with their molecule. Searches were performed in PubMed (for full papers) and Embase (for conference abstracts) to identify primary research articles with information on new and emerging BTK inhibitor molecules identified from the Clinicaltrials.gov searches. The ‘hits’ from these searches were screened to exclude those with irrelevant study topics and study types (e.g. reviews).

**3. New and emerging BTK inhibitors in MCL**

In total, 36 trials were identified on Clinicaltrials.gov that included search terms for BTK inhibitors and MCL. Of these, five were excluded because search terms were present in the introductory text but were not the focus of the clinical trial, and 21 were excluded because they were investigating ibrutinib as the only BTK inhibitor. The remaining 10 trials were confirmed as assessing new and emerging BTK inhibitor molecules (acalabrutinib [ACP-196], BGB-3111, SNS-062, ARQ-531, M7583 and CT-1530). Details of the ongoing clinical trials identified for the new and emerging BTK inhibitors under investigation in MCL are provided in Table 1. Data identified from the targeted literature searches for each of these molecules are summarized below, with the exception of CT-1530 for which no published articles (full papers or conference abstracts) were identified.

### 3.1. Acalabrutinib (ACP-196)

Acalabrutinib inhibits BTK by covalently and irreversibly binding to Cys-481. The  $IC_{50}$  value (concentration where the response is reduced by half) for acalabrutinib against purified BTK is 5.1 nM compared with 1.5 nM for ibrutinib [26]. In cellular assays,  $EC_{50}$  values (concentration that gives the half-maximal response) for acalabrutinib and ibrutinib for inhibition of B-cell receptor (BCR)-induced CD69 expression are 2.9 nM and 0.58 nM, respectively, in peripheral blood mononuclear cells, with comparable results in human whole blood (9.2 nM and 5.8 nM, respectively) [26]. The degree of inhibition of BCR-induced responses (BTK, S6 and ERK phosphorylation) is also similar for these molecules in primary CLL cells [27]. In mice, the  $ED_{50}$  value (dose where the measured effect occurs in at least 50% of samples) for inhibition of CD69 expression in splenocytes was 1.3 mg/kg for acalabrutinib and 2.9 mg/kg for ibrutinib [26]. Pre-clinical anti-tumor effects have been demonstrated for acalabrutinib in terms of reduced cell viability in large B-cell lymphoma cell lines [28], induction of apoptosis in primary CLL cells [27,29] and improved outcomes in a canine B-cell NHL model and two mouse CLL models [30,31]. In healthy volunteers acalabrutinib is rapidly absorbed ( $T_{max}$  [time to maximum plasma concentration of drug] of 0.5–1.0 hours), has a short half-life ( $T_{1/2}$  [time required for elimination of 50% of drug from plasma] of 0.88–2.1 hours), and reaches full target occupancy with a single 100 mg dose [26]. Robust response rates have been reported with acalabrutinib in a phase 1/2 clinical trial in both relapsed or refractory and untreated patients with CLL (NCT02029443) [32,33]. In this trial, the highest rate of BTK occupancy (98%) was observed with twice-daily dosing [33].

Acalabrutinib has fewer off-target effects than ibrutinib. In a panel of 395 non-mutant kinases, 1.5% were inhibited by at least 65% by 1  $\mu$ M acalabrutinib, compared with 8.9% for 1  $\mu$ M ibrutinib [26]. Acalabrutinib also has much lower activity than ibrutinib against kinases with a cysteine in the same position as BTK (TEC family kinases [ITK, TXK, BMX, TEC], EGFR, ERBB2, ERBB4, JAK3 and BLK) and SRC family kinases (FGR, FYN, HCK, LCK, LYN, SRC and YES1) [26]. Indeed,  $IC_{50}$  values for acalabrutinib were below 1000 nM (1  $\mu$ M) for only four kinases other than BTK (ERBB4 [16 nM], BMX [46 nM], TEC [126 nM] and TKX [368 nM]), all of which had substantially lower  $IC_{50}$  values in relation to ibrutinib (ERBB4 [3.4 nM], BMX [0.8 nM], TEC [10.0 nM] and TXK [2.0 nM]) [26]. Ibrutinib has been shown to

also inhibit SRC, LCK and ITK far more potently than acalabrutinib in healthy T cells [27].

No cases of atrial fibrillation have been observed so far in the phase 1/2 clinical trial of acalabrutinib in the 61 patients with relapsed or refractory CLL, after a median follow-up period of 14.3 months (NCT02029443) [32]. Although rates of atrial fibrillation in this study would be influenced by the exclusion of patients with significant cardiovascular disease and electrocardiogram abnormalities, significant cardiovascular disease was also an exclusion criterion in an ibrutinib trial where cases of atrial fibrillation occurred in 10 out of 195 patients (5%) with relapsed or refractory CLL after a median follow-up of 9.4 months, of which six cases (3%) were grade 3 or higher (NCT01578707) [21]. In another trial in patients with relapsed or refractory CLL, where the presence of electrocardiogram abnormalities was an exclusion criterion, atrial fibrillation was reported as a serious AE in 3 (4%) of 85 patients (median follow-up: 20.9 months) (NCT01105247) [34]. In the phase 1/2 trial of acalabrutinib in CLL there have been no cases of atrial fibrillation with acalabrutinib treatment in the 72 patients with treatment-naïve CLL, at a median follow-up of 11 months (NCT02029443) [33]. In a trial of 136 patients with treatment-naïve CLL receiving ibrutinib, 8 (6%) developed atrial fibrillation (1% were grade 3 or higher) at a median follow-up of 17.4 months [35]. Both studies excluded patients with significant cardiovascular disease [33,35].

No cases of major hemorrhage have been reported in the phase 1/2 clinical trial of acalabrutinib in patients with relapsed or refractory (n = 61) or treatment naïve CLL (n = 72) (NCT02029443) [32,33], with the exception of a single grade 3 gastric ulcer bleed due to aspirin use [33]. Clinical trials of ibrutinib have reported grade 3 or higher bleeding in 5% (N = 85; median follow-up: 20.9 months [NCT01105247] [34]) and 1% (N = 195; median follow-up: 9.4 months [NCT01578707] [21]) of patients with relapsed or refractory CLL, and in 4% of patients with treatment naïve CLL (N = 136; median follow-up: 17.4 months [NCT01722487] [35]). The latter two studies [21,35] excluded patients taking warfarin and those with a history of intracranial hemorrhage. In a trial conducted in patients with CLL or small lymphocytic lymphoma (N = 33) who discontinued ibrutinib (median treatment duration: 10.5 months) owing to ibrutinib-attributable AEs, no major hemorrhage was reported with

acalabrutinib treatment at a median follow-up of 9.5 months, including among six patients who previously developed bleeding events while on ibrutinib [22].

Acalabrutinib appears less likely to aggravate or precipitate AEs that lead to ibrutinib discontinuation [22,23].

Headache has been more frequent in acalabrutinib CLL trials (42–43%) [32,33] than in ibrutinib CLL trials (14–18%) [21,34]. All cases of headache reported for acalabrutinib have been grade 1 or 2, have occurred early in treatment and have generally resolved over time, and have not caused any patients to discontinue. Conversely, diarrhea and fatigue have been more common in ibrutinib CLL trials (42–49% and 28–32%, respectively [21,34,35]) than in acalabrutinib CLL trials (35–39% and <15–21%, respectively [32,33]). However, acalabrutinib and ibrutinib have not been directly compared in any head-to-head clinical trials. Such data are necessary to eliminate variations in study design between acalabrutinib and ibrutinib trials that may impact on observed differences in the rates of specific AEs.

In October 2017, the Food and Drug Administration (FDA) approved acalabrutinib for use as a single agent in patients with relapsed or refractory MCL, based on the positive results of a phase 2 study (NCT02213926: Table 1). In this trial, the overall response rate (ORR) for acalabrutinib 100 mg given twice daily to patients with MCL (N = 124) was 81% (complete response in 40%) at a median follow-up of 15.2 months (median duration of response, progression-free survival and overall survival were not reached) [36]. The ORR for ibrutinib 560 mg once daily in the pivotal trial that led to its approval in patients with relapsed or refractory MCL (N = 111) was 68% (complete response in 27%) at a median follow-up of 15.3 months (NCT01236391) [18], although patients in this trial population were more heavily pre-treated and a lower proportion (14%) had low-risk simplified Mantle Cell Lymphoma International Prognostic Index scores than in the acalabrutinib MCL trial (39%) [36].

The most common ( $\geq 20\%$ ) AEs in the acalabrutinib MCL trial were headache (38%), diarrhea (31%), fatigue (27%) and myalgia (21%) [36]. There were no cases of atrial fibrillation and only one serious (grade 3) bleeding event (gastrointestinal [GI]

hemorrhage in one patient with a history of a GI ulcer) [36]. In the ibrutinib MCL trial, the most common ( $\geq 20\%$ ) AEs were diarrhea (50%), fatigue (41%), nausea



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(31%), peripheral edema (28%), dyspnea (27%), constipation (25%), upper-respiratory tract infection (23%) and decreased appetite (21%) [18]. Serious AEs of atrial fibrillation occurred in five patients (5%) and grade 3 bleeding events also occurred in five (5%) patients [18].

Acalabrutinib is also being investigated in combination with BR in patients with untreated MCL (NCT02717624 [phase 1] and NCT02972840 [phase 3]; Table 1), and in more ‘experimental’ combinations with the phosphoinositide 3-kinase inhibitor ACP-319 (NCT02328014 [phase 1/2]) and the immune ‘checkpoint’ inhibitor pembrolizumab (NCT02362035).

3.2. *BGB-3111*

BGB-3111 is an irreversible BTK inhibitor [37,38]. The binding site for this molecule has not (to our knowledge) been made publicly available. BGB-3111 inhibits BTK activity at unspecified nanomolar concentrations in biochemical assays and inhibits BCR-induced responses (BTK auto-phosphorylation and downstream PLC $\gamma$ 2 signalling) in several MCL and diffuse large B-cell lymphoma cell lines [39]. BGB-3111 also has anti-proliferative effects and induces apoptosis in MCL cell lines, and has similar anti-tumor activity to ibrutinib in a subcutaneous MCL xenograft mouse model, but at a much lower dosage (2.5 mg/kg twice daily) versus ibrutinib (50 mg/kg once daily) [39,40].

In a phase 1 study in patients with relapsed or refractory B-cell malignancies, bioavailability of BGB-3111 80 mg once daily was similar to that for ibrutinib 560 mg once daily [37]. In addition, a mean 24 hour BTK occupancy of 98.6% was reported with BGB-3111 40 mg once daily, compared with greater than 90% occupancy reported for acalabrutinib 200 mg once daily [41], which was itself reported as having better target coverage than ibrutinib 420 mg once daily. Of six patients in the phase 1 study who have MCL, four have had an objective response (one complete response) after a median follow-up of 227 days [37]. BGB-3111 is reported as having greater selectivity than ibrutinib for BTK versus EGFR, FGR, FRK, HER2, HER4, ITK, JAK3, LCK, BLK and TEC, although specific values were not able to be identified from the literature [37,39]. No drug-related serious AEs or AEs leading to discontinuation have been observed in the phase

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3 1 trial (N=25) of BGB-3111 in patients with relapsed or refractory B-cell  
4 malignancies, and no cases of grade 3 or 4 bleeding or of atrial fibrillation (including  
5 in four patients with a history of atrial fibrillation) have been reported [37].  
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9 Taken together, the above data indicate that BGB-3111 is a potent inhibitor of BTK,  
10 with potentially better selectivity, bioavailability and target coverage than ibrutinib.  
11 There is one ongoing phase 2 trial of BGB-3111 in patients with relapsed or refractory  
12 MCL (NCT03206970; Table 1), but no data are yet available. Although not the focus  
13 of the clinical trial searches, it is worth noting that a phase 3 trial comparing  
14 BGB-3111 to ibrutinib in patients with Waldenstrom Macroglobulinemia is ongoing  
15 (NCT03053440), and should provide useful information regarding the relative toxicity  
16 of these two drugs.  
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### 24 3.3. M7583

25 M7583 is an irreversible inhibitor of BTK. Where this molecule binds to BTK is not  
26 clearly described in the literature. Nevertheless, it has high potency, with an  $IC_{50}$  of  
27 1.48 nM against purified BTK [42]. M7583 was found to inhibit six (2.2%) of a panel  
28 of 270 kinases by more than 50% (ZAP-70, BLK, BMX, TXK, ITK and SKG) at a  
29 concentration of 1  $\mu$ M [42], which is comparable to the level of enhanced selectivity  
30 exhibited for acalabrutinib versus ibrutinib (inhibition  $\geq 65\%$ ) of 1.5% vs 8.9 of 395  
31 kinases, respectively, at a concentration of 1  $\mu$ M) [26].  
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38 M7583 is reported as having relatively low bioavailability of 16%, a short half-life of  
39 45 minutes, and a high (but unspecified) degree of BTK occupancy after dosing in  
40 mice, and is currently being investigated in patients with relapsed or refractory B-cell  
41 malignancies in a phase 1/2 trial (NCT02825836; Table 1). At the time of reporting,  
42 preliminary data from three subjects (one with MCL) enrolled in this trial showed that  
43 all had an objective response, or stable disease and a relevant clinical benefit [43].  
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### 48 3.4. SNS-062

49 SNS-062 is a non-covalent (reversible) BTK inhibitor. The  $IC_{50}$  value for SNS-062  
50 against purified BTK is 2.9 nM [44], and this molecule has been shown to inhibit  
51 BTK auto-phosphorylation in human whole blood and in mice [44]. In biochemical  
52 assays, SNS-062 exhibited binding to eight kinases at a concentration of less than 25  
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nM, including BTK (0.3 nM) and the TEC kinase family member, ITK (2.2 nM) [44]. SNS-062 has been shown to decrease B-cell activation markers, viability and stromal cell protection in primary CLL cells [45]. Unlike ibrutinib and acalabrutinib, SNS-062 maintains its potent inhibitory activity against both wild-type BTK and cysteine 481 to serine (C481S)-mutated BTK [44,45].

SNS-062 is reported as having good oral bioavailability and tolerability in rats and dogs, with higher continuous drug levels and exposures than ibrutinib [44]. AEs reported in a phase 1 trial of SNS-062 conducted in healthy volunteers included headache in 5 patients (25%) and nausea, bronchitis, fatigue, orthostatic hypotension, and supraventricular tachycardia in one patient (4%) each [46]. There is one ongoing phase 1/2 clinical trial for SNS-062 in patients with B-lymphoid malignancies (NCT03037645; Table 1). No data are yet available for this trial.

3.5. ARQ-531

ARQ-531 is a reversible inhibitor of BTK and has an IC<sub>50</sub> value of 0.85 nM [47]. Treatment with ARQ-531 inhibits BCR-induced responses (BTK, AKT and ERK phosphorylation) in primary CLL cells [48]. However, this molecule demonstrates off-target activity against a number of other kinases, including the majority of SRC and TEC family kinases [48]. ARQ-531 exhibits better activity than ibrutinib in terms of reducing primary CLL cell viability and increasing survival times in a TCL1 mouse model of leukemia [48]. In addition, ARQ-531 has similar IC<sub>50</sub> values against both wild-type and C481S-mutated BTK [48]. Treatment with ARQ-531 also reduces the viability of primary CLL cells from patients with C481S-mutated BTK [48], and has anti-proliferative activity against ibrutinib-resistant SUDHL-4 cells in tissue culture and a xenograft mouse model [47].

In a single oral dose study conducted in monkeys, the bioavailability of 10 mg/kg ARQ-531 was 72.4% [48]. This molecule is being investigated in a phase 1 trial in patients with hematological malignancies (NCT03162536; Table 1). No published data for this clinical trial were identified from our literature searches.

4. BTK inhibitor pipeline in the context of MCL guidelines

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Figure 1 shows the clinical development status of ibrutinib and new and emerging BTK inhibitors in MCL, in the context of National Comprehensive Cancer Network (NCCN) treatment guidelines [49], which are broadly similar to European guidelines with regard to the use of BTK inhibitors [50]. So far, acalabrutinib is the only new BTK inhibitor to be approved in the USA for MCL. Like ibrutinib, this is in patients who have received at least one prior therapy. All other new and emerging BTK inhibitors are being investigated exclusively in this setting. However, most ongoing clinical trials for acalabrutinib and ibrutinib are exploring experimental combinations (in less-aggressive induction and second-line treatment settings) with drugs not approved in MCL, for which data presumably support some synergy with BTK inhibitors, such as B-cell lymphoma 2 (BCL-2) inhibitors [51], programmed cell death protein 1 (PD-1 [checkpoint]) inhibitors [52] and phosphoinositide 3-kinase (PI3K) inhibitors [53-55]. Only ibrutinib is being investigated in patients with MCL in the aggressive induction setting and as a possible third-line treatment following bortezomib failure or relapse following donor stem cell transplant.

## 5. Conclusion

New and emerging BTK inhibitors have the potential to further optimize the treatment of patients with this promising class of molecules. Placement of these drugs among MCL treatment guidelines is likely to evolve substantially over the coming years, as safety and efficacy data from a number of ongoing trials exploring their potential synergy with other drugs, particularly targeted therapies, become available.

## 6. Expert commentary

The available evidence indicates that covalent, irreversible BTK inhibitors being investigated in patients with MCL (acalabrutinib, BGB-311 and M7583) may have similar potency to ibrutinib, but with reduced off-target activity that could translate into improved safety and tolerability. Favourable clinical data for acalabrutinib raise the possibility that efficacy may also be enhanced, possibly as a result of more complete and continuous inhibition of BTK due to its pharmacokinetic and pharmacodynamic properties, although no head-to-head data are available and therefore differences in the trial populations used may be a factor. The potential for improved safety and tolerability seems less likely to apply to non-covalent, reversible BTK inhibitors being investigated in MCL (SNS-062 and ARQ-531), because these

molecules appear to have significant off-target activity against kinases that may be responsible for AEs associated with ibrutinib, including bleeding and atrial fibrillation [56-59]. Where the strengths of these molecules may lie is in their activity against C481S-mutated BTK, although the clinical importance of this mutation in the development of ibrutinib resistance has recently been questioned. Nevertheless, other advantages may well exist for these molecules that cannot be easily deduced from the currently available literature. Indeed, most of the available literature on new and emerging BTK inhibitors pertains to acalabrutinib.

In any of the MCL treatment settings being investigated for ibrutinib, a BTK inhibitor with similar (or better) efficacy but an improved safety and tolerability profile would represent an attractive alternative, providing (at the very least) an avenue to continue BTK inhibitor therapy in patients who would otherwise discontinue. AEs associated with ibrutinib are a major impediment to achieving the best possible outcomes with this breakthrough class of molecules. This is particularly relevant to MCL, where the median age at onset is 68 years, meaning that the majority of patients will require less aggressive induction therapy. Both ibrutinib and acalabrutinib are being investigated in phase 3 trials in this setting in combination with BR (NCT01776840 and NCT02972840, respectively; Figure 1).

Finally, it should be noted that, while data from single arm trials do indicate a more favourable AE profile for acalabrutinib versus ibrutinib, no head-to-head data are yet available. Such data are important for addressing the potential effects of study design variation on observed safety profiles, such as exclusion criteria that could influence rates of bleeding and atrial fibrillation with these drugs. To this end, an ongoing phase 3 head-to-head study of ibrutinib and acalabrutinib in patients with relapsed or refractory CLL (NCT02477696) will be particularly useful in cementing differences in the safety profiles of these drugs that have been hinted at in trials conducted to date.

**7. Five-Year View**

It is expected that several key trials in MCL will read out in the next year or two. This will include the use of BTK inhibition with BR versus BR alone (NCT01776840). If positive, then BTK inhibition will be included in the upfront treatment of patients with MCL. The next logical question is whether the chemotherapy (bendamustine)

component is required, or whether the addition of a CD20 antibody (rituximab) is sufficient. Early data from the MD Anderson Cancer Centre show a response rate of 100% has been achieved when ibrutinib plus rituximab is used upfront. A UK trial comparing rituximab-CHEMO (Bendamustine OR CHOP [cyclophosphamide, doxorubicin, vincristine and prednisone]) with rituximab-ibrutinib as front-line therapy for elderly patients is ongoing. If positive, chemotherapy-free treatment will become the new standard of care for elderly patients. In the relapse setting, BTK inhibition has been combined with BCL-2 inhibition (NCT02471391) and a randomized phase 3 trial has started as well (NCT03112174). If positive, the BTK inhibitor plus BCL-2 inhibitor combination will be a new standard in relapsed or refractory MCL. It could then also be possible to have an upfront chemotherapy free regimen in elderly patients that includes BTK inhibition plus BCL-2 inhibition plus anti-CD20 monoclonal antibody therapy. While no such trials are currently underway, one might expect their initiation in the next few years. The field is truly exciting with novel agents having significant activity.

## 8. Key issues

- Outcomes for patients with mantle cell lymphoma (MCL) have improved with the introduction of upfront aggressive and target therapies, but the disease remains incurable with the possible exception of allograft.
- The clinical benefits of ibrutinib, the first Bruton tyrosine kinase (BTK) inhibitor approved in MCL (as second-line treatment), are becoming clear, but adverse events due to off-target effects warrant refinement of this drug class.
- The available literature suggests that new (acalabrutinib) and emerging (BGB-3111, M7583) covalent, irreversible inhibitors under investigation in MCL have similar potency to ibrutinib, but with fewer off-target effects.
- Non-covalent, reversible BTK inhibitors under investigation in MCL (SNS-062, ARQ-531) may not be as selective as covalent, irreversible inhibitors, but could have activity against some ibrutinib-resistant B-cell malignancies.
- Trials of acalabrutinib, which has now been approved in the USA as second-line treatment for MCL, suggest that both safety and efficacy could be enhanced versus ibrutinib, although no head-to-head data are yet available.

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- Placement of BTK inhibitors in MCL treatment guidelines will likely evolve substantially over the coming years, as the results of trials exploring earlier use of these drugs (e.g. as less-aggressive induction therapy), and their potential synergy with other targeted therapies, become available.

**References**

1. Swerdlow SH, Campo E, Harris N, et al. WHO classification of tumours of the haematopoietic and lymphoid tissues. Lyon: IARC Press; 2008.
2. The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. Blood. 1997; 89(11):3909–3918.
3. Aschebrook-Kilfoy B, Caces DB, Ollberding NJ, et al. An upward trend in the age-specific incidence patterns for mantle cell lymphoma in the USA. Leuk Lymphoma. 2013; 54(8):1677–1683.



4. Zhou Y, Wang H, Fang W, et al. Incidence trends of mantle cell lymphoma in the United States between 1992 and 2004. *Cancer*. 2008; 113(4):791–798.
5. Skibola CF, Bracci PM, Nieters A, et al. Tumor necrosis factor (TNF) and lymphotoxin-alpha (LTA) polymorphisms and risk of non-Hodgkin lymphoma in the InterLymph Consortium. *Am J Epidemiol*. 2010; 171(3):267–276.
6. Smedby KE, Sampson JN, Turner JJ, et al. Medical history, lifestyle, family history, and occupational risk factors for mantle cell lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. *J Natl Cancer Inst Monogr*. 2014; 2014(48):76–86.
7. Tort F, Camacho E, Bosch F, et al. Familial lymphoid neoplasms in patients with mantle cell lymphoma. *Haematologica*. 2004; 89(3):314–319.
8. Wang SS, Slager SL, Brennan P, et al. Family history of hematopoietic malignancies and risk of non-Hodgkin lymphoma (NHL): a pooled analysis of 10 211 cases and 11 905 controls from the International Lymphoma Epidemiology Consortium (InterLymph). *Blood*. 2007; 109(8):3479–3488.
9. Schollkopf C, Melbye M, Munksgaard L, et al. *Borrelia* infection and risk of non-Hodgkin lymphoma. *Blood*. 2008; 111(12):5524–5529.
10. Geisler CH, Kolstad A, Laurell A, et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. *Blood*. 2008; 112(7):2687–2693.
11. Romaguera JE, Fayad LE, Feng L, et al. Ten-year follow-up after intense chemoimmunotherapy with Rituximab-HyperCVAD alternating with Rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. *Br J Haematol*. 2010; 150(2):200–208.
12. Dreyling M, Ferrero S, Hermine O. How to manage mantle cell lymphoma. *Leukemia*. 2014; 28(11):2117–2130.
13. Chiorazzi N, Ferrarini M. B cell chronic lymphocytic leukemia: lessons learned from studies of the B cell antigen receptor. *Annu Rev Immunol*. 2003; 21:841–894.
14. Kupperts R. Mechanisms of B-cell lymphoma pathogenesis. *Nat Rev Cancer*. 2005; 5(4):251–262.



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15. Lenz G, Staudt LM. Aggressive lymphomas. *N Engl J Med.* 2010; 362(15):1417–1429.

16. Honigberg LA, Smith AM, Sirisawad M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. *Proc Natl Acad Sci U S A.* 2010; 107(29):13075–13080.

17. Wang ML, Blum KA, Martin P, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. *Blood.* 2015; 126(6):739–745.

18. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med.* 2013; 369(6):507–516

19. O'Brien S, Furman RR, Coutre SE, et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. *Lancet Oncol.* 2014; 15(1):48–58.

20. Byrd JC, O'Brien S, James, DF. Ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med.* 2013; 369(13):1278–1279.

21. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med.* 2014; 371(3): 213–22.

22. Awan FT, Schuh A, Brown JR, et al. Acalabrutinib monotherapy in patients with ibrutinib intolerance: Results from the phase 1/2 ACE-CL-001 clinical study. *Blood.* 2016; 128(22):638.

23. Shindiapina P, Khountham S, Rogers KA, et al. Natural history of non-infectious, ibrutinib-attributable adverse events leading to alternative BTK inhibitor use in CLL. *Blood.* 2016; 128(22):4385.

24. Maddocks KJ, Ruppert AS, Lozanski G, et al. Etiology of Ibrutinib Therapy Discontinuation and Outcomes in Patients With Chronic Lymphocytic Leukemia. *JAMA Oncol.* 2015; 1(1):80–87.

25. Jain P, Keating M, Wierda W, et al. Outcomes of patients with chronic lymphocytic leukemia after discontinuing ibrutinib. *Blood.* 2015; 125(13):2062–2067.

26. Barf T, Covey T, Izumi R, et al. Acalabrutinib (ACP-196): A covalent Bruton tyrosine kinase (BTK) inhibitor with a differentiated selectivity and in vivo potency profile. *J Pharmacol Exp Ther.* 2017; 363(2):240–252

27. Patel V, Balakrishnan K, Bibikova E, et al. Comparison of Acalabrutinib, A Selective Bruton Tyrosine Kinase Inhibitor, with Ibrutinib in Chronic Lymphocytic Leukemia Cells. *Clin Cancer Res.* 2017;23(14):3734–3743.
28. Koning MT, Ubelhart R, Van Der Zeeuw SAJ, et al. Primary mediastinal large B-cell lymphoma exhibits autonomous BCR signaling and responds to the second generation BTK inhibitor acalabrutinib. *Blood.* 2016; 128(22):4171.
29. Golay J, Ubiali G, Introna M. The specific BTK inhibitor acalabrutinib (ACP-196) shows favorable in vitro activity against chronic lymphocytic leukemia B-cells with CD20 antibodies. *Haematologica.* 2017; 102(10):e400–e403
30. Herman SEM, Montraveta A, Niemann CU, et al. The Bruton Tyrosine Kinase (BTK) Inhibitor Acalabrutinib Demonstrates Potent On-Target Effects and Efficacy in Two Mouse Models of Chronic Lymphocytic Leukemia. *Clin Cancer Res.* 2017; 23(11):2831–2841.
31. Harrington BK, Gardner HL, Izumi R, et al. Preclinical Evaluation of the Novel BTK Inhibitor Acalabrutinib in Canine Models of B-Cell Non-Hodgkin Lymphoma. *PLoS One.* 2016; 11(7):e0159607.
32. Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia. *N Engl J Med.* 2016; 374(4):323–332.
33. Byrd JC, Jones JA, Furman RR, et al. Acalabrutinib, a second-generation bruton tyrosine kinase (Btk) inhibitor, in previously untreated chronic lymphocytic leukemia (CLL). *J Clin Oncol.* 2016; 34(15 Suppl):7521.
34. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med.* 2013; 369(1):32–42.
35. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. *N Engl J Med.* 2015; 373(25):2425–2437.
36. Wang M, Rule S, Zinzani PL, et al. Acalabrutinib in Relapsed or Refractory Mantle Cell Lymphoma: A Single-Arm, Multicenter, Phase 2 Trial. *Lancet.* 2017; in press.
37. Tam C, Grigg AP, Opat S et al. The BTK inhibitor, BGB-3111, is safe, tolerable, and highly active in patients with relapsed/ refractory b-cell malignancies: Initial report of a phase 1 first-in-human trial. *Blood.* 2015; 126(23):832.

38. Tam CS, Opat S, Cull G, et al. Twice daily dosing with the highly specific BTK inhibitor, Bgb- 3111, achieves complete and continuous BTK occupancy in lymph nodes, and is associated with durable responses in patients (pts) with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). *Blood*. 2016; 128(22):642.

39. Li N, Sun Z, Liu Y, et al. BGB-3111 is a novel and highly selective Bruton's tyrosine kinase (BTK) inhibitor. *Cancer Res*. 2015; 75(15 Suppl):2597.

40. Li CJ, Liu Y, Bell T, et al. Novel bruton's tyrosine kinase inhibitor Bgb-3111 demonstrates potent activity in mantle cell lymphoma. *Blood*. 2016; 128(22):5374.

41. Covey T, Barf T, Gulrajani M, et al. ACP-196: A novel covalent Bruton's tyrosine kinase (Btk) inhibitor with improved selectivity and in vivo target coverage in chronic lymphocytic leukemia (CLL) patients. *Cancer Res*. 2015; 75(15 Suppl):2596.

42. Bender AT, Pereira A, Fu K, et al. Btk inhibition treats TLR7/IFN driven murine lupus. *Clinical immunology (Orlando, FL)*. 2016; 164:65–77.

43. Rule S, Tucker D, Kalapur A, et al. Phase I/II, first in human trial of the Bruton's tyrosine kinase inhibitor (BTKi) M7583 in patients with B cell malignancies. *J Clin Oncol*. 2017; 35(15 Suppl):e14101.

44. Binnerts ME, Otipoby KL, Hopkins BT, et al. SNS-062 is a potent noncovalent BTK inhibitor with comparable activity against wild type BTK and BTK with an acquired resistance mutation. *Mol Cancer Ther*. 2015; 14(12 Suppl 2):C186.

45. Fabian CA, Reiff SD, Guinn D, et al. SNS-062 demonstrates efficacy in chronic lymphocytic leukemia in vitro and inhibits C481S mutated Bruton tyrosine kinase. *Cancer Res*. 2017; 77(13 Suppl):1207.

46. Neuman LL, Ward R, Arnold D, et al. First-in-human phase 1a study of the safety, pharmacokinetics, and pharmacodynamics of the noncovalent bruton tyrosine kinase (BTK) inhibitor SNS-062 in healthy subjects. *Blood*. 2016; 128(22):2032.

47. Eathiraj S, Yu Y, Hall T, et al. ARQ 531, a reversible btk inhibitor, demonstrates potent anti-tumor activity in ABC-DLBCL and GCB-DLBCL. *Haematologica*. 2017; 102:574.

- 1  
2  
3 48. Reiff SD, Mantel R, Smith LL, et al. The bruton's tyrosine kinase (BTK)  
4 inhibitor ARQ 531 effectively inhibits wild type and C481S mutant BTK and  
5 is superior to ibrutinib in a mouse model of chronic lymphocytic leukemia.  
6  
7 Blood. 2016; 128(22):3232.  
8  
9 49. National Comprehensive Cancer Network. NCCN clinical practice guidelines  
10 in oncology. Non-Hodgkin's lymphomas. 2016; Available at  
11 [https://www.nccn.org/professionals/physician\\_gls/f\\_guidelines.asp](https://www.nccn.org/professionals/physician_gls/f_guidelines.asp).  
12 2016; Accessed 16 July 2017.  
13  
14 50. Dreyling M, Geisler C, Hermine O, et al. Newly diagnosed and relapsed  
15 mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis,  
16 treatment and follow-up. Ann Oncol. 2014; 25 Suppl 3: iii83-92.  
17  
18 51. Deng J, Isik E, Fernandes SM, et al. Bruton's tyrosine kinase inhibition  
19 increases BCL-2 dependence and enhances sensitivity to venetoclax in chronic  
20 lymphocytic leukemia. Leukemia. 2017; 31(10):2075–2084.  
21  
22 52. Overman MJ, Lopez CD, Benson AB, et al. A randomized phase 2 study of  
23 the Bruton tyrosine kinase (Btk) inhibitor acalabrutinib alone or with  
24 pembrolizumab for metastatic pancreatic cancer (mPC). J Clin Oncol. 2016;  
25 34 (15 Suppl):4130.  
26  
27 53. Gaudio E, Tarantelli C, Spriano F, et al. The novel BTK and PI3K-delta  
28 inhibitors acalabrutinib (ACP-196) and ACP-319 show activity in pre-clinical  
29 B-cell lymphoma models. Eur J Cancer. 2016; 69:S39–S40.  
30  
31 54. Mora-Jensen HI, Niemann CU, Gulrajani M, et al. The combination of ACP-  
32 196 and ACP-319 leads to increased survival in the TCL1-192 CLL mouse  
33 model. Cancer Res. 2016; 76(14 Suppl):4797.  
34  
35 55. Niemann CU, Mora-Jensen HI, Dadashian EL, et al. Combined BTK and  
36 PI3Kdelta inhibition with acalabrutinib and ACP-319 improves survival and  
37 tumor control in CLL mouse model. Clin Cancer Res. 2017; 23(19):5814–  
38 5823.  
39  
40 56. McMullen JR, Boey EJ, Ooi JY, et al. Ibrutinib increases the risk of atrial  
41 fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling.  
42 Blood. 2014; 124(25):3829–3830.  
43  
44 57. Senis YA, Mazharian A, Mori J. Src family kinases: at the forefront of platelet  
45 activation. Blood. 2014; 124(13):2013–2024.  
46  
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58. Atkinson BT, Ellmeier W, Watson SP. Tec regulates platelet activation by GPVI in the absence of Btk. *Blood*. 2003; 102(10):3592–3599.

59. Hamazaki Y, Kojima H, Mano H, et al. Tec is involved in G protein-coupled receptor- and integrin-mediated signalings in human blood platelets. *Oncogene*. 1998; 16(21):2773–2779.

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**Table 1.** Details of ongoing clinical trials of new and emerging Bruton tyrosine kinase inhibitors in patients with mantle cell lymphoma.

Study ID	Intervention	Condition	Phase	Primary endpoint(s)	N	Completion <sup>a</sup>	Approvals
NCT02213926	Acalabrutinib	R/R MCL	2	ORR (at least 1 year)	124	Feb 2017	FDA (Oct 2017)
NCT02328014	Acalabrutinib + ACP-319	NHL, MM and B-ALL <sup>b</sup>	1/2	AEs (up to 1 year)	126 <sup>c</sup>	Aug 2017	None
NCT02981745	CT-1530	R/R BCNHL, CLL, MCL, WM, MZL, DFCL and DLBCL	1/2	DLTs (28 days) MTD and/or RP2D	200 <sup>c</sup>	Sep 2018	None
NCT03037645	SNS-062	R/R CLL, LL, MCL, SLL and WM	1/2	MTD and/or RP2D (up to 21 months) ORR (up to 24 months)	124 <sup>c</sup>	Sep 2018	None
NCT03206970	BGB-3111	R/R MCL	2	ORR (up to 3 years)	80 <sup>c</sup>	Nov 2018	None
NCT03162536	ARQ-531	R/R BCL, DLBCL, SLL, CLL, MCL, WM	1	AEs (up to 28 weeks) RP2D (up to 24 weeks)	120 <sup>c</sup>	Dec 2018	None
NCT02825836	M7583	R/R BCM, MCL and DLBCL	1/2	DLTs (up to 28 days) BOR (up to 6 months)	60 <sup>c</sup>	Oct 2019	None
NCT02717624	Acalabrutinib + BR	Untreated and R/R MCL	1b	TEAEs (timeframe unclear)	48 <sup>c</sup>	Feb 2021	None
NCT02362035	Acalabrutinib + Pembrolizumab	NHL, MM, HL, CLL, RS, WM <sup>b</sup>	1b/2	TEAEs (2 years)	159	Apr 2021	None
NCT02972840	Acalabrutinib + BR vs placebo + BR	Untreated MCL	3	PFS (48 months)	546 <sup>c</sup>	Oct 2022	None

AE, adverse event; B-ALL, B-cell acute lymphocytic leukemia; BCL, B-cell lymphoma; BCM, B-cell malignancies; BCNHL, B-cell non-Hodgkin lymphoma; BOR, best overall response; BR, bendamustine + rituximab; CLL, chronic lymphocytic leukemia; DFCL, diffuse follicle center lymphoma; DLBCL, diffuse large B-cell lymphoma; DLTs, dose-limiting toxicities; HL, Hodgkin lymphoma; LL, lymphoplasmacytoid lymphoma; MCL, mantle cell lymphoma; MM, multiple myeloma; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; ORR, overall response rate; PFS, progression-free survival; RP2D, recommended phase 2 dose; R/R, relapsed or refractory; RS, Richter's syndrome; SLL, small lymphocytic leukemia; TEAE, treatment-emergent adverse event; WM, Waldenstrom macroglobulinemia.

<sup>a</sup> Estimated primary completion date.

<sup>b</sup> MCL not specifically mention among listed conditions, but was included among keywords submitted for the study.

<sup>c</sup> Estimated enrolment number.

NCCN guideline placement	Treatment	Phase 1	Phase 1/2	Phase 2	Phase 3	Approved
Aggressive induction	ibrutinib (maintenance)			NCT02242097		
	ibrutinib + R-DHAP or R-DHAOx	NCT02055924 <sup>a</sup>				
	ibrutinib + R-CHOP	NCT01569750 <sup>a</sup>				
Less aggressive induction	Acalabrutinib + BR	NCT02717624 <sup>a</sup>			NCT02972840	
	ibrutinib + BR				NCT01776840	
	ibrutinib + LR			NCT03232307		
	Acalabrutinib + ACP-319		NCT02328014 <sup>a,b</sup>			
	Acalabrutinib + pembrolizumab		NCT02362035 <sup>a,b</sup>			
Second-line	ibrutinib + pembrolizumab		NCT03153202 <sup>a,b</sup>			
	ibrutinib	NCT00849654 <sup>a</sup>		NCT01238391	NCT01804686	November 2013
	Acalabrutinib			NCT02213926		October 2017
	ibrutinib + venetoclax	NCT02419560		NCT02471391	NCT03112174	
	ibrutinib vs lenvatinib				NCT01646021	
	BGB-3111			NCT03209970		
	ibrutinib + R			NCT01880567		
	ibrutinib + LR	NCT02446236		NCT02460276		
	ibrutinib + ol			NCT02736617		
	Acalabrutinib + ACP-319		NCT02328014 <sup>a,b</sup>			
	Acalabrutinib + pembrolizumab		NCT02362035 <sup>a,b</sup>			
	CT-1530		NCT02981745 <sup>a</sup>			
	SNS-062		NCT03037645 <sup>a</sup>			
	M783		NCT02825838 <sup>a</sup>			
	ARQ-531		NCT03162538 <sup>a</sup>			
	ibrutinib + bortezomib		NCT02358458			
	ibrutinib + obinutuzumab + GDC-0199		NCT02558816			
	ibrutinib + ublituximab		NCT02441312 <sup>a</sup>			
	ibrutinib + ixazomib		NCT02441312 <sup>a</sup>			
	ibrutinib + pembrolizumab	NCT02441312 <sup>a</sup>				
	ibrutinib + carfilzomib		NCT02441312 <sup>a</sup>			
	ibrutinib + cimetuzumab		NCT03088878 <sup>a</sup>			
	Acalabrutinib + BR	NCT02717624 <sup>a</sup>				
	ibrutinib + lenalidomide	NCT01955499 <sup>a</sup>				
	ibrutinib + BR	NCT01478042 <sup>a</sup>				
	ibrutinib + BR + venetoclax	NCT03295240				
	ibrutinib + palbociclib	NCT02159755				
	ibrutinib + selinexor	NCT02303392 <sup>a</sup>				
	ibrutinib + umbralisib	NCT02268851 <sup>a</sup>				
	ibrutinib + buparlisib	NCT02756247 <sup>a</sup>				
Third-line and beyond	ibrutinib (after bortezomib)			NCT01599949		
	ibrutinib (after DSCT)			NCT01599633 <sup>a</sup>		

BR, bendamustine + rituximab; DSCT, donor stem cell transplant; L/R, lenalidomide/rituximab; NCCN, National Comprehensive Cancer Network; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; R-DHAP, rituximab + dexamethasone + cytarabine + cisplatin; R-DHAOx, rituximab + dexamethasone + cytarabine + oxaliplatin

<sup>a</sup> Includes treated and untreated patients.

<sup>b</sup> MCL not specifically mention among listed conditions, but was included among keywords submitted for the study.

<sup>c</sup> Malignancies other than MCL also included in the trial population.

**Figure 1.** Trials of bruton tyrosine kinase (BTK) inhibitors in the context of National Comprehensive Cancer Network (NCCN) guidelines for the treatment of mantle cell lymphoma (MCL). New and emerging BTK inhibitors are highlighted in bold black text. Red text indicates drugs that are being tested in combination with BTK inhibitors that are not currently recommended anywhere in NCCN treatment guidelines for MCL. Molecules within blue (rather than green) arrows are BTK inhibitors where there is reasonable evidence of enhanced BTK selectivity that could translate into improved safety and tolerability over ibrutinib in an equivalent indication under investigation. Clinical trials of new and emerging BTK inhibitors were identified from the results of the initial ClinicalTrials.gov search (presented in Table 1). Clinical trials of ibrutinib were identified using a supplementary search for trials including terms for ibrutinib AND MCL. Unless otherwise indicated, trials are in patients with MCL only.



NCCN guideline placement	Treatment	Phase 1	Phase 1/2	Phase 2	Phase 3	Approved
Aggressive induction	Ibrutinib (maintenance)			NCT02242097		
	Ibrutinib + R-DHAP or R-DHAOx	NCT02055924 <sup>c</sup>				
	Ibrutinib + R-CHOP	NCT01569750 <sup>c</sup>				
Less aggressive induction	<b>Acalabrutinib + BR</b>	NCT02717624 <sup>a</sup>			NCT02972840	
	Ibrutinib + BR				NCT01776840	
	Ibrutinib + LR			NCT03232307		
	<b>Acalabrutinib + ACP-319</b>		NCT02328014 <sup>a,b</sup>			
	<b>Acalabrutinib + pembrolizumab</b>		NCT02362035 <sup>a,b</sup>			
	Ibrutinib + pembrolizumab		NCT03153202 <sup>a,c</sup>			
Second-line	Ibrutinib	NCT00849654 <sup>b</sup>		NCT01236391	NCT01804686	November 2013
	<b>Acalabrutinib</b>			NCT02213926		October 2017
	Ibrutinib + venetoclax	NCT02419560		NCT02471391	NCT03112174	
	Ibrutinib vs temsirolimus				NCT01646021	
	<b>BGB-3111</b>			NCT03206970		
	Ibrutinib + R			NCT01880567		
	Ibrutinib + LR	NCT02446236		NCT02460276		
	Ibrutinib + obinutuzumab			NCT02736617		
	<b>Acalabrutinib + ACP-319</b>		NCT02328014 <sup>a,b</sup>			
	<b>Acalabrutinib + pembrolizumab</b>		NCT02362035 <sup>a,b</sup>			
	<b>CT-1530</b>		NCT02981745 <sup>b</sup>			
	<b>SNS-062</b>		NCT03037645 <sup>c</sup>			
	<b>M7583</b>		NCT02825836 <sup>c</sup>			
	<b>ARQ-531</b>		NCT03162536 <sup>c</sup>			
	Ibrutinib + bortezomib		NCT02356458			
	Ibrutinib + obinutuzumab + GDC-0199		NCT02558816			
	Ibrutinib + ublituximab		NCT02013128 <sup>c</sup>			
	Ibrutinib + Ixazomib		NCT03323151			
	Ibrutinib + pembrolizumab	NCT02950220 <sup>c</sup>		NCT03153202 <sup>a,c</sup>		
	Ibrutinib + carfilzomib		NCT02269085			
	Ibrutinib + cirmutuzumab		NCT03088878 <sup>c</sup>			
	<b>Acalabrutinib + BR</b>	NCT02717624 <sup>a</sup>				
	Ibrutinib + lenalidomide	NCT01955499 <sup>c</sup>				
	Ibrutinib + BR	NCT01479842 <sup>c</sup>				
	Ibrutinib + BR + venetoclax	NCT03295240				
	Ibrutinib + palbociclib	NCT02159755				
	Ibrutinib + selinexor	NCT02303392 <sup>c</sup>				
	Ibrutinib + umbralisib	NCT02268851 <sup>c</sup>				
	Ibrutinib + buparlisib	NCT02756247 <sup>c</sup>				
Third-line and beyond	Ibrutinib (after bortezomib)			NCT01599949		
	Ibrutinib (after DSCT)			NCT02869633 <sup>c</sup>		

BR, bendamustine + rituximab; DSCT, donor stem cell transplant; L/R, lenalidomide/rituximab; NCCN, National Comprehensive Cancer Network; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; R DHAP, rituximab + dexamethasone + cytarabine + cisplatin; R-DHAOx, rituximab + dexamethasone + cytarabine + oxaliplatin

a Includes treated and untreated patients.

b MCL not specifically mention among listed conditions, but was included among keywords submitted for the study.

c Malignancies other than MCL also included in the trial population.

Figure 1. Trials of bruton tyrosine kinase (BTK) inhibitors in the context of National Comprehensive Cancer Network (NCCN) guidelines for the treatment of mantle cell lymphoma (MCL). New and emerging BTK inhibitors are highlighted in bold black text. Red text indicates drugs that are being tested in combination with BTK inhibitors that are not currently recommended anywhere in NCCN treatment guidelines for MCL.

Molecules within blue (rather than green) arrows are BTK inhibitors where there is reasonable evidence of enhanced BTK selectivity that could translate into improved safety and tolerability over ibrutinib in an equivalent indication under investigation. Clinical trials of new and emerging BTK inhibitors were identified from the results of the initial ClinicalTrials.gov search (presented in Table 1). Clinical trials of ibrutinib were identified using a supplementary search for trials including terms for ibrutinib AND MCL. Unless otherwise

168x154mm (300 x 300 DPI)



indicated, trials are in patients with MCL only.

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